

## Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment

Patrick J. Brennan, MD, PhD,\* Tito Rodriguez Bouza, MD,\* F. Ida Hsu, MD, David E. Sloane, MD, and Mariana C. Castells, MD, PhD *Boston, Mass*

**Background:** Rapid desensitization, a procedure for graded drug administration, allows for the safe readministration of a medication after certain types of hypersensitivity reactions (HSRs) and is indicated in cases in which there are no reasonable therapeutic alternatives. The use of rapid desensitization for HSRs to mAbs has not been validated.

**Objective:** We sought to describe our experience with rapid desensitization to mAbs, including rituximab, infliximab, and trastuzumab.

**Methods:** One hundred five rapid desensitizations were performed in 23 patients with a standardized 12-step, 6-hour protocol. Our approach to patient evaluation before desensitization is described. The severity, characteristics, and timing of both initial HSRs and HSRs during desensitization were determined by means of retrospective review of medical records. After a reaction during desensitization, patient-specific protocol modifications were made before each subsequent desensitization.

**Results:** 104 of 105 desensitizations undertaken were successfully completed. We observed HSRs during 29% of desensitizations, including 27 mild reactions, 1 moderate reaction, and 2 severe reactions. Overall, reactions during desensitization were markedly less severe than initial HSRs, but reactions did recur in a minority of successive desensitizations.

**Conclusions:** Rapid desensitization is a promising method for the delivery of monoclonal therapeutics after an HSR, but the possibility of a reaction remains with each desensitization. (*J Allergy Clin Immunol* 2009;124:1259-66.)

**Key words:** Allergy, rapid desensitization, adverse drug reaction,

*drug allergy, monoclonal antibody, anaphylaxis, hypersensitivity reaction, rituximab, infliximab, trastuzumab*

More than 100 years after Paul Ehrlich described the notion of a specific “immune body” to explain the observed effect of antiserum in the treatment of infectious disease<sup>1</sup> and more than 30 years after the development of the hybridoma for mAb production,<sup>2</sup> therapeutic mAbs have become the fastest-growing segment of the pharmaceutical industry.<sup>3</sup> Not unexpectedly, we have observed an increasing number of referrals for reactions to these agents.

Reactions to mAbs vary by agent and include acute idiosyncratic infusion, serum sickness-type, cutaneous, and anaphylactic reactions.<sup>4</sup> Reactions that raise concern for immediate hypersensitivity are common during mAb infusion, and such reactions have been reported for chimeric, humanized, and “fully human” monoclonal therapeutics. Urticaria, for example, has been reported in up to 15% of mAb infusions.<sup>5</sup> The rate of infusion reactions clinically consistent with immediate hypersensitivity is 5% to 10% for rituximab,<sup>6</sup> 2% to 3% for infliximab,<sup>7-9</sup> and 0.6% to 5% for trastuzumab.<sup>10,11</sup> Immediate hypersensitivity reactions (HSRs) have also been reported for omalizumab,<sup>12,13</sup> natalizumab,<sup>14</sup> basiliximab,<sup>15,16</sup> abciximab,<sup>17,18</sup> and cetuximab.<sup>19</sup>

Reactions that are clinically consistent with Gell and Coombs type I hypersensitivity<sup>20</sup> might be circumvented through rapid desensitization, a process that involves gradually increasing the rate and concentration of medication administration over several hours.<sup>21</sup> Mast cells, basophils, or both are thought to be the major cells targeted by rapid desensitization, and experimental desensitization models render these cells unresponsive to antigen but not to other activating stimuli.<sup>22,23</sup> Proposed mechanisms for this unresponsiveness include modification of the stoichiometry of IgE-antigen binding,<sup>24</sup> FcεRI receptor internalization and down-regulation,<sup>25</sup> and alteration of cellular signaling pathways.<sup>22,26</sup> Rapid desensitization has been safely and widely used for antibiotics and aspirin, and experience with desensitization to other medications continues to grow. This process has been invaluable in allowing the use of life-saving and disease-modifying medications in situations in which there is no acceptable treatment alternative. Desensitization has been described in case reports or small series for rituximab,<sup>27</sup> infliximab,<sup>28-30</sup> trastuzumab,<sup>31,32</sup> muronoma,<sup>33</sup> cetuximab,<sup>34</sup> and omalizumab.<sup>12</sup> No desensitization-related deaths have been reported.

Herein we report our experience with desensitization to rituximab, infliximab, and trastuzumab. This is, to our knowledge, the largest collection of mAb desensitizations reported to date. Desensitization was undertaken in 23 patients, with a total of 105 desensitization procedures performed. We describe the rapid desensitization process in detail, including the initial clinical

From the Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital.

\*These authors contributed equally to this work.

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Reprint requests: Mariana Castells, MD, PhD, One Jimmy Fund Way, Smith Building, Room 626D, Boston, MA 02115. E-mail: mcastells@partners.org.

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**Abbreviation used**

HSR: Hypersensitivity reaction  
mAb: Monoclonal antibody

evaluation, characteristics of the patients who have undergone desensitization, the desensitization process, reactions during desensitization, and modification of the desensitization protocol for subsequent desensitizations.

**METHODS****Patient evaluation before desensitization**

This collaboration between investigators at the Dana Farber Cancer Institute and the Brigham and Women's Hospital Rheumatology, Immunology, and Allergy and Medical Intensive Care Divisions was approved by the Brigham and Women's Hospital Human Research Committee (institutional review board protocol no. 2007-P-000050/1). Between September 2003 and March 2009, patients with known HSRs to mAbs, including rituximab, infliximab, and trastuzumab, were referred to the allergy service for rapid desensitization. All patients desensitized to mAbs at our institution during this period are included in this report, including 4 patients who were included in previous publications.<sup>27,31</sup>

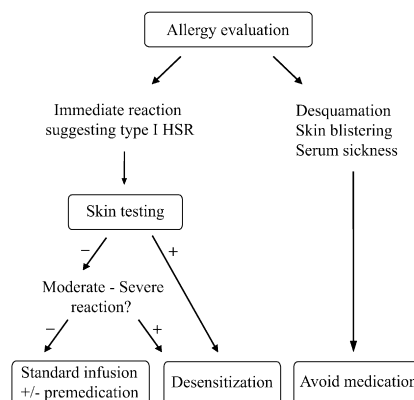
Our evaluation process before desensitization is presented in Fig 1. We recommended medication avoidance if the clinical picture was consistent with erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or serum sickness. We did not offer rapid desensitization for delayed maculopapular exanthem. Fever was not an exclusion criterion, but desensitization was not considered for reactions reported to be fever alone. Although fever is not a feature of type I hypersensitivity, in a subset of patients, fever was associated with reactions that were otherwise consistent with immediate hypersensitivity.

**Classification of reactions**

Data were obtained by means of retrospective review of the electronic medical record. HSRs were classified as mild, moderate, or severe according to the classification system proposed by Brown.<sup>35</sup> Fever, chills, or both, which are not included in the Brown classification, were classified as mild for subjective fever or a measured temperature of less than 38.0°C. A temperature of greater than 38.0°C was classified as a moderate reaction. Signs and symptoms of HSRs were classified as cutaneous (flushing, pruritus, urticaria, and angioedema), cardiovascular (chest pain, tachycardia, sense of impending doom, presyncope, syncope, and hypotension), respiratory (dyspnea, wheezing, and oxygen desaturation), throat tightness, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), neurological/muscular (vision disturbances, back and neck pain, and numbness/weakness), and fever/chills. Reactions were included that occurred during or within 6 hours of mAb infusion.

**Skin testing for hypersensitivity**

Patients with a history suggestive of type I hypersensitivity underwent skin testing with the offending agent. Skin testing was performed at least 3 weeks after the initial reaction to minimize the likelihood of false-negative results. Monoclonal antibody was obtained as full-strength solution (rituximab) or reconstituted per the manufacturer's instructions and was diluted further in normal saline for intradermal testing. For epicutaneous skin testing, a drop of rituximab (10 mg/mL), infliximab (10 mg/mL), or trastuzumab (21 mg/mL) was applied to the volar surface of the forearm, followed by pricking with a Quintest device (Bayer, Spokane, Wash). For intradermal injections, we empirically chose to use 0.03 mL of a 1:100 dilution of the mAb full-strength solution (concentrations as above), followed, if the result was negative, by a 1:10 dilution. Skin tests were performed at least 3 weeks after the initial HSRs to minimize false-negative results. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control (diluent). Histamine prick (10 mg/mL) was used as a positive control.



**FIG 1.** Evaluation of a patient for desensitization. At the initial evaluation, patients with reactions that were not thought to be amenable to desensitization were excluded. Patients with symptoms suggestive of a Gell and Coombs type I HSR, including pruritus, urticaria, flushing, chest tightness, wheezing, nausea, dizziness, or neuromuscular symptoms, were evaluated by means of skin testing. If skin test results were positive, desensitization was offered. If skin test results were negative, the decision whether to offer desensitization was based on the severity of the initial reaction and clinical judgment.

In the case of a positive skin test result, rapid desensitization was recommended. Because the sensitivity of skin testing with mAbs is not known, if the results of skin testing were negative, the decision of whether to offer desensitization was based on the severity of the initial reaction. If the results of skin testing were negative after a mild initial reaction, we recommended a standard infusion with premedication targeted toward the specific symptoms experienced. If the initial reaction was moderate to severe, we recommended readministration through rapid desensitization.

**Twelve-step rapid desensitization protocol**

Our standardized desensitization protocol has been described.<sup>27,31,36</sup> A sample desensitization protocol is shown in Table 1. Based on our prior experience with desensitization to small-molecule chemotherapeutics, diphenhydramine or hydroxyzine (25 mg administered orally or intravenously) and either famotidine (20 mg administered intravenously) or ranitidine (50 mg administered intravenously) were administered 20 minutes before the initiation of the protocol. Acetaminophen or glucocorticoids were not routinely used as premedication but were added in some cases, as determined based on standard oncology or rheumatology protocols.  $\beta$ -Adrenergic blocking medications were held for 24 hours before desensitization.

Three solutions (each 250 mL in water with 5% dextrose) were delivered in 12 consecutive steps, each step increasing the rate of drug administration by 2- to 2.5-fold. Solution 1 was a 100-fold dilution of the final target concentration (steps 1-4), solution 2 was a 10-fold dilution of the final target concentration (steps 5-8), and the concentration of solution 3 was calculated by subtracting the cumulative dose administered in steps 1 to 8 from the total target dose (steps 9-12). Steps 1 to 11 each took 15 minutes, and step 12 was prolonged to complete the target dose. Initial desensitizations occurred in the medical intensive care unit with 1-to-1 nursing. All subsequent mAb infusion was administered by means of desensitization, and subsequent desensitizations were carried out on an oncology inpatient floor or in an outpatient infusion center always with 1-to-1 nursing. The interval between chemotherapy treatments was determined by the patient's oncologist or rheumatologist and varied from 1 week to 3 months. Treatment schedules and concomitant medication administration were based on the underlying disease and were not altered for desensitization.

**Treatment of reactions during desensitization**

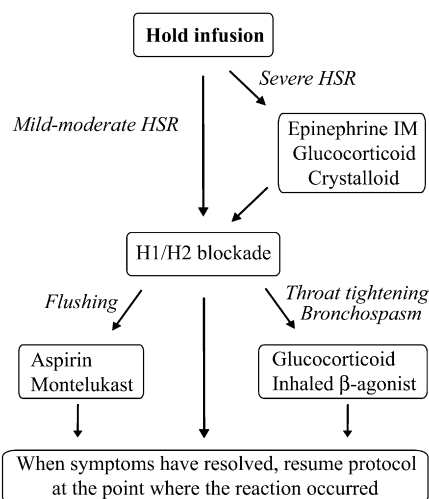
The management of reactions during desensitization is presented in Fig 2. Treatment was aimed at blocking the local and systemic effects of mast cell mediators, including histamine, prostaglandins, and leukotrienes. The

**TABLE I.** Desensitization protocol for intravenous infliximab (600 mg)

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.012	0.012
2	1	5.0	15	1.25	0.030	0.042
3	1	10.0	15	2.50	0.060	0.102
4	1	20.0	15	5.00	0.120	0.222
5	2	5.0	15	1.25	0.300	0.522
6	2	10.0	15	2.50	0.600	1.122
7	2	20.0	15	5.00	1.200	2.322
8	2	40.0	15	10.00	2.400	4.722
9	3	10.0	15	2.50	5.953	10.675
10	3	20.0	15	5.00	11.906	22.580
11	3	40.0	15	10.00	23.811	46.392
12	3	80.0	174.38	232.50	553.609	600.000
Total time = 340 min (5.66 h)						

Solution 1, 0.024 mg/mL; solution 2, 0.24 mg/mL; solution 3, 2.38 mg/mL.

Standard premedications included diphenhydramine, 25 mg administered intravenously, and famotidine, 20 mg administered intravenously, 20 minutes before desensitization. Medications at the bedside included intramuscular epinephrine (1:1000, 0.3 mg); diphenhydramine, 25 to 50 mg administered intravenously; famotidine, 20 mg administered intravenously; methylprednisolone, 50 mg administered intravenously; aspirin, 325 mg administered orally; montelukast, 10 mg administered orally; albuterol, 2 puffs; and lorazepam, 0.5 mg administered intravenously.



**FIG 2.** Management of reactions during desensitization. The infusion was held for all reactions. Severe reactions were treated aggressively, as shown. Histamine H<sub>1</sub> and H<sub>2</sub> blockade was administered for all reactions. For flushing or airway symptoms, specific treatment was initiated, as depicted.

infusion was promptly held for all reactions. Severe reactions were treated with the administration of intramuscular epinephrine available at the bedside plus intravenous crystalloid or glucocorticoids if indicated. All reactions were treated with histamine (H<sub>1</sub> and sometimes H<sub>2</sub>) blockade. If multiple reactions occurred during a single desensitization, repeated doses of H<sub>1</sub>-antihistamines were administered. Bronchospasm was treated with inhaled β-agonists and intravenous glucocorticoids. Symptoms of throat tightness were also treated with intravenous glucocorticoids if not rapidly relieved by antihistamines. Anxiety, either before or during desensitization, was treated with a low-dose benzodiazepine.

## RESULTS

### Patient characteristics

Twenty-three patients were treated with desensitization. Characteristics of the patients who underwent desensitization are

presented in Table II. Indications for treatment were hematologic malignancy (11/23), rheumatologic disease (8/23), breast cancer (3/23), and idiopathic thrombocytopenia purpura (1/23). Fifty-seven percent of patients desensitized were female. The rate of atopy, defined as a history of allergic rhinitis, allergic conjunctivitis, suspected allergic asthma, food allergy, or atopic dermatitis/eczema, was 50%.

For infliximab and trastuzumab, the majority of HSRs were observed after multiple exposures. Interestingly, for 5 of 9 patients with reactions to either of these agents, the initial reaction was observed on the first or second re-exposure after an interruption in therapy and after a well-tolerated treatment course. In contrast, 11 of 14 patients who were ultimately desensitized to rituximab experienced a reaction on the first exposure.

In most cases epicutaneous and intradermal skin tests were performed, although patients evaluated for rituximab hypersensitivity before 2005 were not routinely skin tested. Only 1 patient had a positive result on epicutaneous testing, and this was after a reaction to trastuzumab. On intradermal testing, a positive wheal-and-flare reaction was observed in 4 of 6 patients tested with infliximab, 2 of 2 patients tested with trastuzumab, and 6 of 9 patients tested with rituximab.

### Characteristics of initial reactions

Twenty of 23 of the initial reactions occurred during single-agent therapy. The 3 remaining patients had received multiple agents but reacted during infusion of the mAb and during re-exposure to the same mAb. The severity of initial reactions to rituximab, infliximab, and trastuzumab is presented in Fig 3, A. Considering all 3 agents together, 26% of the reactions were mild, 48% were moderate, and 26% were severe. Two of the initial reactions to rituximab required treatment in an intensive care setting, both involving respiratory compromise.

Characteristics of initial patient reactions are presented in Fig 4, A. Reactions were classified by the involvement of the following signs or symptoms: cutaneous, cardiovascular, respiratory,

TABLE II. Patient characteristics

Agent	Age/sex	Indication	Atopy	Reaction	Skin test result	No. of desensitizations
Trastuzumab	28/F	Breast cancer	Yes	Re-exposure	+	8
Trastuzumab	37/F	Breast cancer	Yes	Re-exposure	+	10
Trastuzumab	52/F	Breast cancer	Yes	Re-exposure	+	11
Infliximab	20/F	RA	Yes	5th	+	2
Infliximab	22/M	JRA	No	7th	+	2
Infliximab	23/M	RA	Yes	7th	+	3
Infliximab	43/F	Psoriatic arthritis	No	Re-exposure	+	4
Infliximab	53/F	IBD-related arthritis	Yes	>10th	—	4
Infliximab	76/M	Psoriatic arthritis	Yes	Re-exposure	—	6
Rituximab	63/M	NHL	No	1st	+	5
Rituximab	73/M	NHL	No	1st	+	5
Rituximab	70/F	NHL	Yes	1st	+	2
Rituximab	61/F	CLL	No	1st	+	5
Rituximab	65/M	CLL	Yes	1st	+	9
Rituximab	56/F	Waldenstrom's	Yes	1st	+	1
Rituximab	43/F	ITP	No	1st	—	7
Rituximab	43/M	NHL	Yes	1st	—	5
Rituximab	34/M	FL	No	1st	—	1
Rituximab	27/M	BMT	No	1st	ND	2
Rituximab	39/M	NHL	No	1st	ND	1
Rituximab	54/F	Polymyositis	No	3rd	ND	8
Rituximab	64/F	NHL	No	4th	ND	2
Rituximab	23/F	SLE	Yes	Re-exposure	ND	2

*Re-exposure* is defined as reaction on re-exposure after a prolonged, well-tolerated course.

RA, Rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; IBD, inflammatory bowel disease; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; ITP, idiopathic thrombocytopenic purpura; FL, follicular lymphoma; BMT, bone marrow transplantation; ND, not determined; SLE, systemic lupus erythematosus.

throat tightness, fever/chills, gastrointestinal, or neurologic/muscular. If present, multiple signs or symptoms were included for a single reaction. A cutaneous reaction was observed as a component of almost 70% of initial reactions and was the most frequently observed type of reaction overall, followed by cardiovascular reactions, respiratory reactions, and throat tightness.

### Reactions during desensitization

Overall, reactions during desensitization were much less severe than initial reactions (Fig 3, B). Reactions were observed during 30 (29%) of 105 desensitizations, and 90% of these reactions were mild. We previously reported a reaction rate of 33% during desensitization to small-molecule chemotherapeutics.<sup>27</sup> Reactions were seen in 3 of 23 desensitizations performed in patients with negative skin test results and 15 of 67 desensitizations performed in patients with positive skin test results. Two severe reactions were observed during the course of multiple desensitizations, and both patients had positive skin test results. One reaction during trastuzumab desensitization occurred during the tenth desensitization. This patient had throat tightness and respiratory distress with documented hypoxemia, the prior 7 desensitizations having been reaction free. After this reaction, the patient declined to complete the infusion. The patient's initial reaction to trastuzumab, which was graded as moderate, consisted of hives, flushing, and mild chest tightness with stable vital signs. The other severe reaction, this one to infliximab, occurred during the second desensitization and was characterized by hypotension. After treatment and the rapid resolution of hypotension, the

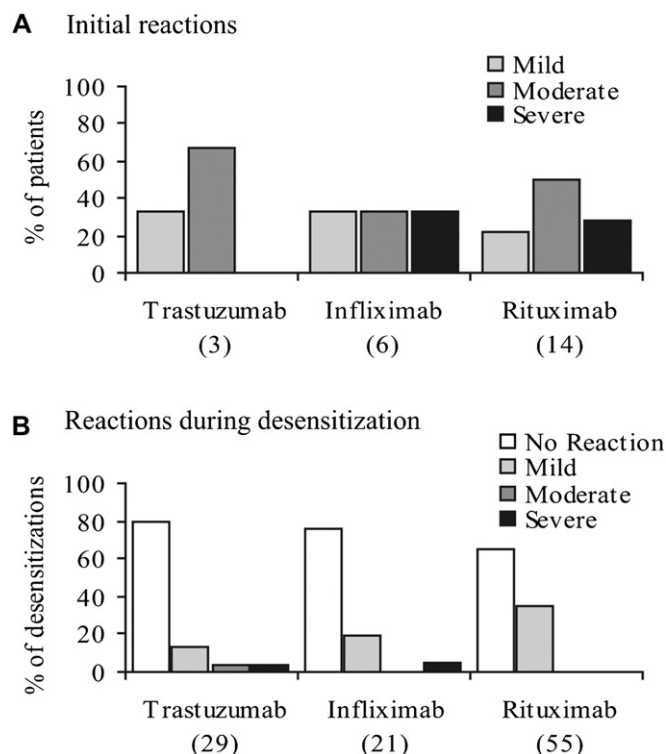
infusion was completed per protocol. This patient's initial reaction was also severe and characterized by hypotension. Of note, the patient's first desensitization was uneventful.

As presented in Fig 4, B, cutaneous reactions were the most frequent type of reaction documented during desensitization. No blistering skin reactions were observed. Although the last step (step 12) of the protocol constitutes approximately 51% of the total time of desensitization and administers approximately 92% of the total dose of medication, 70% of reactions during desensitization occurred during this step (Fig 5), which is similar to our previously published experience with chemotherapeutic agents.<sup>27</sup> No reactions were observed during the first 7 steps of desensitization to any mAb. Two delayed reactions were observed after desensitization, one after rituximab and the other after trastuzumab. Both delayed reactions occurred within 24 hours of desensitization, were mild, and were managed by telephone.

### Protocol modification and reactions over multiple desensitizations

In the event of a reaction during a prior desensitization, the standard 12-step protocol was used as a starting point in the establishment of a patient-specific protocol. We adopted a two-fold approach to protocol modification for subsequent desensitizations. The first component involves the addition of scheduled medications administered either as premedications or between specific steps during desensitization. For all reactions, we added antihistamines at least one full step before the point at which the reaction occurred. For example, if a patient reacted at step 11, we typically added an antihistamine between steps 9 and 10. We used





**FIG 3.** Severity of initial reactions and reactions during desensitization. **A**, The percentage of patients with mild, moderate, and severe reactions is presented by agent for the initial reaction, with the total number of patients for each agent shown in parentheses after the name of the agent. **B**, Reactions during desensitization were graded as mild, moderate, severe, or no reaction and are presented as a percentage of total desensitizations for a given agent. The number of desensitizations for each agent is shown in parentheses after the name of the agent.

montelukast and aspirin as premedications for cutaneous reactions, including flushing.<sup>37</sup> For bronchospasm, a glucocorticoid and montelukast were added as premedications. For chills and fever, acetaminophen and a glucocorticoid were added as premedications.

The second component of our approach to protocol modification involved the addition or lengthening of steps before the step at which a reaction was observed. For example, if a patient had urticaria during step 8, a new step (step 7a) could be added with an infusion rate between that of steps 7 and 8. This approach was used when a patient reacted despite additional premedications, as described above. The rate of reaction over multiple successive desensitizations is presented in Fig 6.

## DISCUSSION

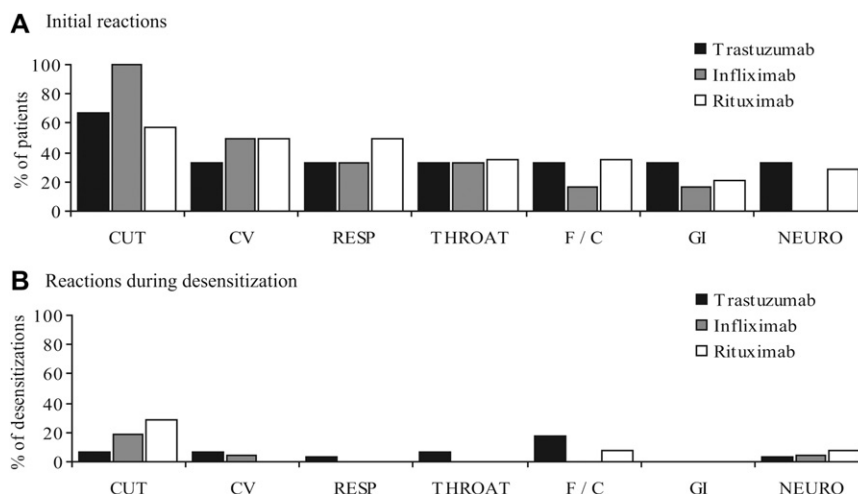
This report describes our experience with 105 rapid desensitizations in 23 patients receiving treatment with rituximab, infliximab, and trastuzumab. Rapid desensitization is highly successful, and to date, we have been able to complete all but one of the mAb desensitizations undertaken. Unlike patients desensitized to antibiotics, the majority of patients treated with mAb therapeutics require interval drug administration. Our protocol allows for single-day outpatient desensitization performed in a hospital-associated infusion center with specially trained 1-to-1 nursing.

Immunologic reactions to mAbs are likely to differ mechanistically from reactions to small-molecule therapeutics. Both the half-life and dosing interval for mAbs might be longer than for traditional small-molecule therapeutics. Because mAbs are proteins and are relatively large molecules, they can act as complete T- and B-cell antigens and do not require haptenation, as would a small-molecule therapeutic. Therapeutic mAbs can be divided into 4 subtypes: fully murine, chimeric (approximately 30% murine), humanized (approximately 5% murine), and fully human. Rituximab and infliximab are chimeric mAbs, whereas trastuzumab is humanized. A decrease in antigenicity is expected with a decrease in murine protein sequence, but even a fully human antibody contains nonnative epitopes and can elicit an immunologic response. Both anti-murine and anti-idiotypic antibodies directed against monoclonal therapeutics have been observed.<sup>15,38-40</sup> The development of antibodies directed against the monoclonal-target complex has also been demonstrated.<sup>41</sup>

As with small-molecule therapeutics, reactions to mAbs are likely to include both on-target and off-target effects. Most therapeutic mAbs recognize cell-surface receptors, and the engagement of these receptors can lead to signaling, cytokine release, complement activation, and cell death. It is likely that some infusion reactions to monoclonal therapeutics are due to target-dependent biologic effects. Supporting this notion, standard infusion reactions to rituximab are thought to correlate with disease burden and therefore “target” burden.<sup>42</sup> Fevers, although not classically considered to be a feature of immediate hypersensitivity, were observed in this report as a feature of reactions that were otherwise suggestive of type I Gell and Coombs hypersensitivity. Fevers, which are also commonly observed in the absence of reactions consistent with immediate hypersensitivity, might be due to on-target or off-target effects of monoclonal therapeutics. Alternatively, because mast cells produce TNF- $\alpha$  and other pyrogens,<sup>43</sup> the fevers observed might have been part of an IgE- or mast cell-mediated reaction.

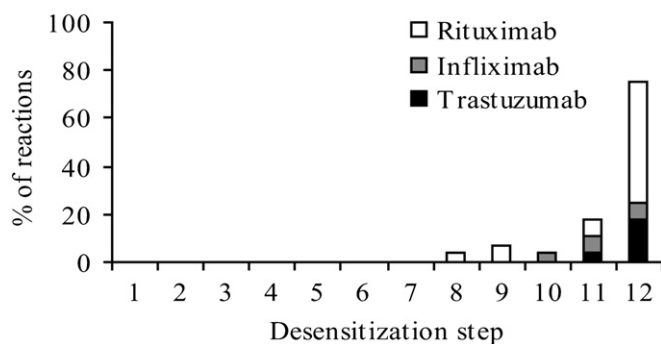
None of the patients who underwent desensitization to rituximab was known to have been treated previously with other monoclonal therapeutics. It is surprising and somewhat unexpected that the majority of anaphylactic-type reactions to rituximab occurred on the first exposure. Xenogenic sensitization to murine protein might explain our observed reactivity pattern.<sup>44-48</sup> Sensitization to unexpectedly cross-reactive antigens might also lead to preformed IgE in the absence of drug exposure. For example, pre-existing glycopeptide-specific IgE-mediated reactions have been described for cetuximab.<sup>49</sup> Infusion reactions might also be caused by an excipient or contaminant in the infusate to which a patient was previously sensitized, as has been demonstrated for omalizumab.<sup>13</sup>

In this report HSRs were observed during 29% of desensitizations. As we have observed with small-molecule chemotherapeutics, the majority of reactions occurred during the final step of desensitization. Although we have observed reactions in the early stages of the protocol with small-molecule chemotherapeutics, we have not observed reactions during desensitization to mAbs during the first 7 steps. Should this trend continue as we accrue more data, we will consider elimination of premedications or early steps in the desensitization protocol. Protocol modification for subsequent desensitization is designed around the notion that mast cell activation requires surpassing a threshold antigen concentration, administration rate, or both. Toward that end, a



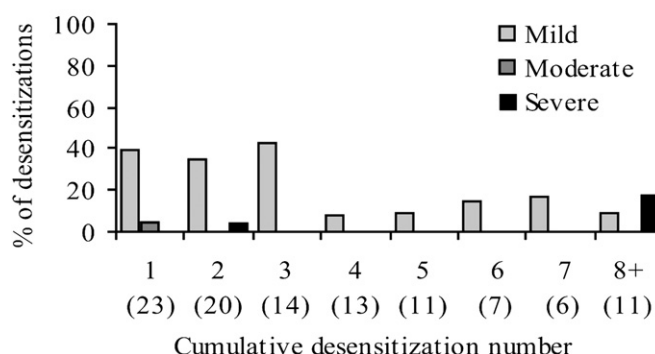
**FIG 4.** Characteristics of initial reactions and reactions during desensitization. The characteristics of reactions are depicted by agent for the initial reaction (**A**) and for reactions during desensitization (**B**). Data in Fig 4, **B**, are expressed as percentages of the total desensitizations performed for each agent. *CUT*, Cutaneous; *CV*, cardiovascular; *RESP*, respiratory; *THROAT*, throat tightness; *F/C*, fever/chills; *GI*, gastrointestinal; *NEURO*, neurologic/muscular.

#### Reactions by step number



**FIG 5.** Timing of reactions during desensitization. The steps at which reactions occurred among 30 reactions during desensitization are shown as a percentage of all reactions. One patient with an extended protocol reacted in the final step, and this reaction was included under step 12.

#### Reactions over multiple desensitizations



**FIG 6.** Reactions over multiple desensitizations. The frequency of reactions at each desensitization number is presented. The number of patients who reached each number of desensitizations is indicated in parentheses.

major component of protocol modification involves the addition of scheduled medications, such as antihistamines, which might work by blocking mast cell mediators at a point in the protocol at which the antigen would have precipitated a clinical reaction. In our prior report of 413 desensitizations, mostly to small-molecule chemotherapeutics, we reported a rapid reduction in the rate of reactions with multiple desensitizations, with reaction rates being less than 5% by the sixth desensitization. We have been less successful in reducing the rates of reaction to mAbs after multiple desensitizations. We have observed reactions in 27% of desensitizations performed for 8 or more courses, and 1 of these reactions was severe.

Although a subset of patients continue to have reactions during successive desensitizations, suggesting persistent medication hypersensitivity, repeat desensitization might not be required for each drug infusion in all patients. The relatively long half-life of monoclonal therapeutics might allow maintenance of the desensitized state. Repeated desensitization might also result in

the induction of long-term tolerance, even in the absence of circulating mAb. For one patient included in this report, after several uneventful desensitizations to rituximab, skin test results converted from positive to negative. Rituximab was subsequently tolerated through standard infusion with no reaction. In another patient, however, although trastuzumab skin test results converted to negative on the day after desensitization, skin test results were again positive one week after desensitization. Interestingly, Melamed and Stahlman<sup>32</sup> reported the apparent induction of tolerance to trastuzumab in one of two patients treated with desensitization in conjunction with subcutaneous rush immunotherapy.

Important limitations to the interpretation of the data presented in this report should be acknowledged. We cannot predict how patients would have responded to readministration without desensitization. Consideration of this point is particularly relevant because standard infusion reactions to rituximab, for example, are generally most problematic with the first dose and decrease thereafter.<sup>5</sup> Additionally, we do not know the sensitivity and

specificity of skin testing for the mAbs used in desensitization. Although the reaction rate was lower during desensitization for patients who had negative skin test results, reactions were seen in both those with positive skin test results and those with negative skin test results. Skin testing data for small-molecule chemotherapeutics, however, suggest that patients with positive skin test results will react during readministration by means of standard methods and that a reaction prevents delivery of the full dose.<sup>50</sup> Although positive skin test results are suggestive of an IgE-mediated mechanism, we have not yet demonstrated the presence of monoclonal-specific IgE in our patient population. Reduced mAb efficacy in the setting of a suspected immunologic response is also a concern because drug-specific IgG has been associated with a reduction in clinical response for infliximab,<sup>7</sup> adalimumab,<sup>51</sup> and natalizumab.<sup>14</sup> Of note, Duburque et al<sup>28</sup> demonstrated significant clinical responses in a majority of patients after HSRs to infliximab and subsequent desensitization. Despite these limitations, our rapid desensitization protocol has allowed for the safe administration of mAbs to patients who otherwise would not have been treated.

In summary, rapid desensitization is a promising method for the administration of an mAb after a reaction that is clinically consistent with type I hypersensitivity. A trained allergist should be involved in evaluation of the initial reaction and all subsequent desensitization procedures because there exists the possibility of a severe reaction on subsequent desensitization, even after an uneventful desensitization. Rapid desensitization is an important option for the continued use of monoclonal therapeutics after an HSR in cases in which there is no suitable alternative.

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**Clinical implications: Rapid desensitization is a promising method for the delivery of mAbs after an immediate HSR and should be considered when there are no acceptable therapeutic alternatives.**

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